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Gene	Reaction(s) catalyzed in vitro	Reaction(s) catalyzed in vivo	Gene	Reaction(s) catalyzed in vitro	Reaction(s) catalyzed in vivo
PIK3C3	PI → PI(3)P	PI → PI(3)P	PTPMT1	PI(5)P → PI	Phosphatidylglycerophosphate → Phosphatidylglycerol
PIK3C2A	PI → PI(3)P, PI(4)P → PI(3,4)P ₂ , PI(4,5)P ₂ → PI(3,4,5)P ₃	PI → PI(3)P, PI(4)P → PI(3,4)P ₂	FIG4	PI(3,5)P ₂ → PI(3)P, PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(3,5)P ₂ → PI(3)P
PIK3C2B	PI → PI(3)P, PI(4)P → PI(3,4)P ₂ , PI(4,5)P ₂ → PI(3,4,5)P ₃	PI → PI(3)P	OCRL	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(4,5)P ₂ → PI(4)P
PIK3C2G	PI → PI(3)P, PI(4)P → PI(3,4)P ₂	–	INPP5B	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(4,5)P ₂ → PI(4)P
PIKFYVE	PI → PI(5)P, PI(3)P → PI(3,5)P ₂	PI → PI(5)P, PI(3)P → PI(3,5)P ₂	INPP5D	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(3,4,5)P ₃ → PI(3,4)P ₂
PIP4K2A	PI(3)P → PI(3,4)P ₂ → PI(3,4,5)P ₂ , PI(5)P → PI(4,5)P ₂	PI(5)P → PI(4,5)P ₂	INPP5E	PI(3,5)P ₂ → PI(3)P, PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂
PIP4K2B	PI(3)P → PI(3,4)P ₂ , PI(5)P → PI(4,5)P ₂	PI(5)P → PI(4,5)P ₂	INPP5F	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(3,4,5)P ₃ → PI(3,4)P ₂
PIP4K2C	PI(5)P → PI(4,5)P ₂	–	INPP5J	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(3,4,5)P ₃ → PI(3,4)P ₂
PIK3CA	PI → PI(3)P, PI(4)P → PI(3,4)P ₂ , PI(4,5)P ₂ → PI(3,4,5)P ₃	PI(4,5)P ₂ → PI(3,4,5)P ₃	INPP5K	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(3,4,5)P ₃ → PI(3,4)P ₂
PIK3CB	PI → PI(3)P, PI(4)P → PI(3,4)P ₂ , PI(4,5)P ₂ → PI(3,4,5)P ₃	PI(4,5)P ₂ → PI(3,4,5)P ₃	INPPL1	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂	PI(4,5)P ₂ → PI(4)P, PI(3,4,5)P ₃ → PI(3,4)P ₂
PIK3CD	PI → PI(3)P, PI(4)P → PI(3,4)P ₂ , PI(4,5)P ₂ → PI(3,4,5)P ₃	PI(4,5)P ₂ → PI(3,4,5)P ₃	SACM1L	PI(3)P → PI, PI(4)P → PI	PI(4)P → PI
PIK3CG	PI → PI(3)P, PI(4)P → PI(3,4)P ₂ , PI(4,5)P ₂ → PI(3,4,5)P ₃	PI(4,5)P ₂ → PI(3,4,5)P ₃	SYNJ1	PI(3)P → PI, PI(4)P → PI, PI(4,5)P ₂ → PI(4)P	PI(4,5)P ₂ → PI(4)P
IPMK	PI(4,5)P ₂ → PI(3,4,5)P ₃	PI(4,5)P ₂ → PI(3,4,5)P ₃	SYNJ2	PI(4,5)P ₂ → PI(4)P	–
PIP5K1A	PI → PI(5)P, PI(3)P → PI(3,4)P ₂ → PI(3,4,5)P ₂ , PI(3)P → PI(3,5)P ₂ , PI(4)P → PI(4,5)P ₂ , PI(3,4)P ₂ → PI(3,4,5)P ₃	PI(4)P → PI(4,5)P ₂	DGKA	DAG → PA	DAG → PA
PIP5K1B	PI → PI(5)P, PI(3)P → PI(3,4)P ₂ → PI(3,4,5)P ₂ , PI(3,4)P ₂ → PI(3,4,5)P ₃	PI(4)P → PI(4,5)P ₂	DGKB	DAG → PA	DAG → PA
PIP5K1C	PI(3)P → PI(3,4)P ₂ → PI(3,4,5)P ₂ , PI(3)P → PI(3,5)P ₂ , PI(4)P → PI(4,5)P ₂ , PI(3,4)P ₂ → PI(3,4,5)P ₃	PI(4)P → PI(4,5)P ₂	DGKG	DAG → PA	DAG → PA
PI4K2A	PI → PI(4)P	PI → PI(4)P	DGKD	DAG → PA	DAG → PA
PI4K2B	PI → PI(4)P	PI → PI(4)P	DGKE	DAG → PA	DAG → PA
PI4KA	PI → PI(4)P	PI → PI(4)P	DGKZ	DAG → PA	DAG → PA
PI4KB	PI → PI(4)P	PI → PI(4)P	DGKH	DAG → PA	DAG → PA
MTM1	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	DGKQ	DAG → PA	DAG → PA
MTMR1	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	–	DGKI	DAG → PA	DAG → PA
MTMR2	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	PI(3)P → PI	DGKK	DAG → PA	DAG → PA
MTMR3	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	PI(3,5)P ₂ → PI(5)P	EIF2AK3	DAG → PA	DAG → PA
MTMR4	PI(3)P → PI	PI(3)P → PI	AGK	DAG → PA, MAG → LPA	DAG → PA, MAG → LPA
MTMR6	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	PI(3,5)P ₂ → PI(5)P	SPHK1	Sphingosine → Sphingosine 1-phosphate	Sphingosine → Sphingosine 1-phosphate
MTMR7	PI(3)P → PI	–	SPHK2	Sphingosine → Sphingosine 1-phosphate	Sphingosine → Sphingosine 1-phosphate
MTMR8	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	PI(3)P → PI	CERK	Ceramide → Ceramide 1-phosphate	Ceramide → Ceramide 1-phosphate
MTMR14	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	PI(3)P → PI, PI(3,5)P ₂ → PI(5)P	PPAP2A	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Sphingosine	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Ceramide, Sphingosine 1-phosphate → Sphingosine
PTEN	PI(3)P → PI, PI(3,4)P ₂ → PI(4)P, PI(3,5)P ₂ → PI(5)P, PI(3,4,5)P ₃ → PI(4,5)P ₂	PI(3,4,5)P ₃ → PI(4,5)P ₂	PPAP2B	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Sphingosine	PA → DAG, LPA → MAG, Sphingosine 1-phosphate → Sphingosine
TPST2	PI(3)P → PI, PI(3,4)P ₂ → PI(4)P, PI(3,5)P ₂ → PI(5)P, PI(3,4,5)P ₃ → PI(4,5)P ₂	PI(4,5)P ₂ → PI(4)P, PI(3,4)P ₂ → PI(3,4)P ₂	PPAP2C	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Sphingosine	PA → DAG, LPA → MAG, Sphingosine 1-phosphate → Sphingosine
TMEM55A	PI(4,5)P ₂ → PI(5)P	–	PPAPDC1A	PA → DAG, LPA → MAG, DGPP → PA	–
TMEM55B	PI(4,5)P ₂ → PI(5)P	PI(4,5)P ₂ → PI(5)P	PPAPDC1B	PA → DAG, LPA → MAG, DGPP → PA	–
INPP4A	PI(3,4)P ₂ → PI(3)P	PI(3,4)P ₂ → PI(3)P	PPAPDC2	PSDP → PSMP, FDP → FMP, PA → DAG	PSDP → PSMP
INPP4B	PI(3,4)P ₂ → PI(3)P, PI(3,4,5)P ₃ → PI(3,5)P ₂	PI(3,4)P ₂ → PI(3)P	LPIN1	PA → DAG	PA → DAG
			LPIN2	PA → DAG	PA → DAG
			LPIN3	PA → DAG	–
			SGPP1	Sphingosine 1-phosphate → Sphingosine	Sphingosine 1-phosphate → Sphingosine

SnapShot: Lipid Kinases and Phosphatases

Cell

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This SnapShot presents the mammalian proteins that have been identified as enzymes that catalyze the phosphorylation or dephosphorylation of lipid substrates. We have included both the in vitro and in vivo reactions reported in the literature to highlight the importance of assessing the data from both sources.

We have limited the results from in vitro experiments to those published using full-length native or recombinant proteins; consequently, we have not included those reactions catalyzed by nonregulated, isolated catalytic domains. For the in vivo data, in addition to reports in which accurate measurements of the lipid substrates and products have been performed in cells, we have included the reactions identified using indirect measurements made using fluorescently tagged proteins expressed in cells that bind specifically to the lipid substrate and/or product in question.

The differences between the in vitro and in vivo reactions catalyzed by some lipid kinases and phosphatases further illustrates the importance of in vivo validation of enzyme reactions measured in the test tube.

Several reasons could explain differences in substrate specificity of a lipid kinase or phosphatase measured in a living cell or animal, compared to a test tube assay: (1) the cellular localization of the enzyme and, consequently, the access that the kinase or phosphatase has to its lipid substrate; (2) the unique membrane and protein environment in which the lipid substrate is presented to the enzyme; and (3) the presence of regulatory proteins and lipids in the cell that could determine which lipid substrates are engaged in vivo but that could be absent from an in vitro assay.

Furthermore, the technical challenges associated with accurately measuring the products of lipid kinase and phosphatase reactions in vivo could also contribute and, in some cases, could explain why similar in vivo data has not been reported.

Phospholipids are made up of different fatty acid moieties at the sn1 and sn2 position of the glycerol backbone and indeed can have acyl, alkyl, or alkenyl linkages; thus, for any given phospholipid, multiple molecular species exist that differ in the length and saturation of the fatty acid moieties. New methodologies in mass spectrometry are now revealing that the products of lipid kinase reactions measurable in vivo, such as PI(3,4,5)P₃, are limited to only a few molecular species, suggesting that the kinases and phosphatases that are responsible for PI(3,4,5)P₃ metabolism are selective for different molecular species.

Although this SnapShot has focused on the phosphatases that antagonize the actions of the lipid kinases, the products of the kinase reactions can in some cases be degraded by alternative activities. For example, sphingosine-1-phosphate can be degraded by a lysase activity. Furthermore, PI(4,5)P₂ and PA can be metabolized by phospholipase enzymes: phosphoinositide-specific phospholipase C hydrolyses PI(4,5)P₂ to generate DAG and inositol (1,4,5)P₃, and phospholipase A₁ and A₂ hydrolyse PA to generate LPA.

ABBREVIATIONS

PI, phosphatidylinositol; PI(3)P, phosphatidylinositol 3-phosphate; PI(4)P, phosphatidylinositol 4-phosphate; PI(5)P, phosphatidylinositol 5-phosphate; PI(3,4)P₂, phosphatidylinositol 3,4-bisphosphate; PI(3,5)P₂, phosphatidylinositol 3,5-bisphosphate; PI(4,5)P₂, phosphatidylinositol 4,5-bisphosphate; PI(3,4,5)P₃, phosphatidylinositol 3,4,5-trisphosphate; PA, phosphatidic acid; LPA, lyso-phosphatidic acid; DAG, diacylglycerol; MAG, monoacylglycerol; DGPP, diacylglycerol pyrophosphate; PSDP, presqualine diphosphate; PSMP, presqualine monophosphate; FDP, farnesyl diphosphate; FMP, farnesyl monophosphate.

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